REMARKS

Claims 2 to 38 are pending in this application. Claim 1 was previously canceled. Applicants have amended claims 2, 20, 21, and 38 to address informalities. Claim 21 was also amended to recite use of an RNA dependent DNA polymerase to perform a reverse transcription reaction in step d). The specification has been amended to reflect the proprietary nature of all trademarks recited in the application and to correct obvious typographical errors. The amendments are supported throughout the specification and claims as originally filed and therefore, add no new matter to the application.

Applicants acknowledge the Examiner's withdrawal of prior rejections of claims 2 to 38 for nonstatutory, obviousness-type double patenting and consideration of the Information Disclosure Statement filed on March 15, 2010.

Rejections under 35 U.S.C. § 103(a)

Claims 2 to 38 were rejected as allegedly unpatentable over Ziman *et al.* (U.S. 2004/0081978; "Ziman") in view of Godfrey *et al.* (U.S. Patent No. 7,101,663; "Godfrey"). The Office characterizes Ziman as disclosing all elements recited in claim 2 except that of producing a first or second strand cDNA in a reaction that is completed in 45 minutes or less before citing Godfrey in an attempt to provide a rapid reverse transcription method that is completed in about 10 minutes (*see*, the Office Action dated October 13, 2009 at pages 5 and 6). In response to applicants' previous reply filed on March 15, 2010, the Office newly alleges that Ziman also describes producing amplified RNA from double stranded cDNA by *in vitro* transcription using a DNA dependent RNA polymerase that initiates transcription from a first promoter sequence in a reaction that is completed in 270 minutes or less (*see*, the Office Action dated June 16, 2010 at pages 2 and 3). Applicants respectfully traverse this rejection for at least the following reasons.

First, contrary to the Office's assertion, Ziman does not disclose, or even suggest, a step of producing amplified RNA from double stranded cDNA by *in vitro* transcription in a reaction that is completed in 270 minutes or less, or 180 minutes or less as recited in independent claim 2. The Office has not indicated where a skilled practitioner can find a description or suggestion of

such a step in Ziman or Godfrey. As explained in the previous reply, Ziman discloses that his methods require *in vitro* transcription incubation times of 16 hours (*see, e.g.*, ¶¶ [0057] and [0222]). A reduction of at least 14 hours in such a method is significant and surprising (as explained further below), and it cannot fairly be dismissed as a matter of "routine optimization."

In addition, while claim 2 recites that the first two steps to produce double-stranded cDNA must be completed in 90 minutes or less, Ziman reports on completing his cDNA synthesis reaction in 120 minutes (*see,* ¶ [0219]). This difference also distinguishes the presently claimed methods from the Office's references. Additional incubation steps required by Ziman amount to an extra 35 minutes (*see,* ¶¶ [0217] and [0220]). Thus, the main steps in Ziman's method take 18 hours (1080 minutes), and the entire process takes at least 18 hours and 35 minutes. Comparing only the main steps, Ziman takes 1080 minutes, and applicants' claim 2 recites steps a), b), and c) that are completed in less than 270 minutes (and dependent claim 20 recites a total time of less than 230 minutes). Thus, Ziman's method takes at least four times longer than applicants' claimed method.

The Office has added Godfrey in an attempt to arrive at the claimed methods, however, Godfrey describes only a rapid reverse transcription reaction that is completed in about 10 minutes. Even if skilled practitioners were for the sake of argument to combine the disclosures of Godfrey and Ziman (and nothing of record suggest doing so), Godfrey might at best reduce only the processing time of step (a) of claim 2. Godfrey does not describe producing a second strand cDNA or producing amplified RNA from the double stranded cDNA by in vitro transcription.

Applicants respectfully submit that no skilled practitioner reading Ziman would have even considered reducing the over 18 hours of processing time required in Ziman's method down to only 270 minutes or less as presently claimed, while still expecting to obtain useful amplification results as described in the present application. The difference between Ziman's method and that presently claimed cannot justifiably be dismissed as merely "routine optimization." One of skill in the art would have no reason to believe that the reaction times

could be performed in as little time as presently recited in applicants' claim 2. As explained in the present specification (page 8, lines 3-9):

> ... the reduction in reaction times by terminating the reaction and/or moving onto the next action reflects a truncation in the amount of time available for the production of various reaction products. Thus the use of "completed" in the above means that a reaction is terminated or that the next reaction begins. This reflects the surprising observation that such decreased time periods are sufficient to produce material sufficient to permit amplification without significant differences in the observed level of amplification (emphasis added).

Thus, applicants' claimed methods allow efficient amplification of RNA in far less time than what a skilled practitioner would have expected to be required to produce an adequate amount of amplified RNA. The Office has not provided any evidence to suggest otherwise, nor is there anything in Ziman or Godfrey that would have led a skilled practitioner to believe that the claimed methods with very rapid reaction times would work at all to amplify RNA. Accordingly, the rejection should be withdrawn.

Further, applicants submit that it is improper to combine the quantitative RT-PCR methods of Godfrey with the RT-PCR methods of Ziman. The short processing times of Godfrey cannot simply be applied to Ziman's methods as the Office proposes. In particular, Ziman uses random primers to amplify an entire mRNA message (*see, e.g.*, ¶¶ [0011], [0032] to [0034], [0041], and [0043] to [0045]). In contrast, Godfrey uses specific primers in his rapid PCR methods. Godfrey clearly states that "the specificity of any given PCR reaction relies heavily, but not exclusively, on the identity of the primer sets" (*see*, 6:7-8). Godfrey also describes the use of high concentrations of "PCR primer sets specific to the cDNA" and "reverse-transcriptase-optimized and PCR-optimized primers" to achieve optimal results (*see*, 6:58, 59, and 65). For example, Godfrey uses specific primers that anneal to CEA and β-GUS (*see*, Examples 3 and 4; and Tables 1 and 3), which were designed to span a junction between specific exons of mRNA. Apparently, the only reference in Godfrey to the use of a random primer is in Example 1, in a test of the effect of a wax layer on the ability of the system to detect fluorescence (*see*, 16:46-55). This description is totally irrelevant to an analysis of obviousness of the present claims.

The Office alleges that skilled practitioners would have somehow picked the method described in Godfrey, without regard to the context of Godfrey or Ziman, to make a substitution in Ziman. Applicants submit that this is not a fair reading of Godfrey. If one of ordinary skill in the art were to consider Godfrey at all, it would be with an understanding of the significant differences between the random primers used in RT-PCR, as described by Ziman, and the specific primer sets used in quantitative RT-PCR, as described by Godfrey. Skilled practitioners would not have been motivated by these references, or anything else in the art, to modify the method described in Ziman in an attempt to arrive at applicants' claimed method. Further, even if these references were combined, the resulting combination would still not provide the method recited in claim 2. For at least the same reasons, claims 3 to 38, which depend from claim 2, are also patentable. Accordingly, applicants respectfully request that the present rejection be reconsidered and withdrawn.

CONCLUSION

Applicants submit that the pending claims are allowable and request early and favorable action thereon. Applicants do not concede any positions of the Office that are not expressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

The Petition for One-Month Extension of Time fee ($130) is being paid on the electronic filing system by way of deposit account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 26370-0052US1.

Respectfully submitted,

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